Catherine Rahilly-Tierney M.D., M.P.H Expert Witness Report

May 10, 2019

Introduction

I, Catherine Rahilly-Tierney, M.D., M.P.H., was engaged by counsel at Williams & Connolly LLP, to serve as an expert witness in the cases brought by Cuyahoga County, Ohio and Summit County, Ohio, which have been consolidated in *In re: National Prescription Opiate Litigation*, MDL No. 2804. I understand that my opinions will be offered on behalf of Cardinal Health and certain other distributor defendants in these cases. My opinions set forth in this report are based upon my background, training, education, experience, and my review of the medical literature, among other things. A list of the materials that I rely upon in this report is attached.

In addition, my opinions set forth in this report are stated to a reasonable degree of professional certainty. I reserve the right to supplement or amend this report upon review of additional materials or information provided to me by the parties in this case, any other materials or information that may become available, and/or at the request of counsel for additional analyses. I further reserve the right to offer opinions within my area of expertise in response to additional opinions and/or subjects offered or addressed by other experts on behalf of the Plaintiffs. If asked to more fully explain my opinions as expressed in this report, I reserve the right to rely on other portions of the documents that I have cited, relied upon, or discussed or that I have not already explicitly used in this report. At trial, I may rely on visual aids and may rely on analogies concerning my opinions in this report.

I am being compensated for my time spent working on this matter based on my hours actually expended at the rate of $300 per hour. My compensation is in no way linked to the outcome of this matter or the content of my testimony.

I. Background, education, and qualifications

I am an Instructor in Medicine at Harvard Medical School, an Associate Epidemiologist at Brigham & Women's Hospital, an Assistant Professor in Medicine at Boston University, and a Staff Physician at VA Boston Healthcare System. I received an M.D. from the University of Rochester School of Medicine and Dentistry in 2002, and completed clinical training in Internal Medicine at Mount Sinai Medical Center in 2005. Between 2005 and 2007, I completed the Fellowship in Faculty Development and General Internal Medicine receiving an M.P.H. from the Harvard School of Public Health in 2007. Between 2007 and 2009, I completed a fellowship in Preventive Cardiology at the VA Boston. I have published numerous articles in the peer-reviewed medical literature, which I have listed in my curriculum vitae at the end of the Opinion.

As a population scientist specializing in the analysis of complex observational and claims databases, I began research consulting in 2012. As consultants, myself and a select team of biostatisticians, health economists, programmers, clinicians, and epidemiologists assist clients in state government and the biotechnology and pharmaceutical industries by directing projects that use extant datasets to examine the efficacy of novel genetic tests and drugs, review state-sponsored research programs, and link and analyze complex observational datasets to study disease associations. In 2014 participated in a comprehensive review of the Kentucky Lung Cancer Research Program, a $60 million endeavor funded using Kentucky's share Master Settlement Agreement with participating tobacco companies. More recently, we have been working with the Massachusetts Department of Public Health (MDPH) to link records of ambulance attendances of opioid overdoses from the Massachusetts Ambulance Trip

Information System with emergency department records submitted to MDPH's Syndromic Surveillance program, in an effort to better understand characteristics and dispositions of persons treated for overdose. In a separate project, we have linked person-level records from Massachusetts Department of Transportation Crash Data System with case-mix (hospital and emergency department records) data from across the state and are using the linked data to analyze the impact of substance use, including opioids, on severity of injury in a crash as measured by hospital charges, length of stay, and other parameters.

Throughout my fellowships and as a consultant, I have continued on a part-time basis to regularly care for complex patients in emergency department, primary care, and inpatient settings. I am board-certified in internal medicine and currently treat a primary care panel of about 300 patients once a week in an outreach clinic of the Boston VA, and supervise housestaff caring for medical inpatients on the wards at the West Roxbury VA Hospital. I have experienced first-hand a clinical culture that has shifted from patient-centered, in which we as physicians concern ourselves with the nature and treatment of pain in our own patients as a "fifth vital sign," to a treatment approach motivated by prevention of adverse outcomes in a population that largely differs from that whom we treat directly in our clinic for chronic pain.

II. Definitions of terms

Medical use of prescription opioids is use that does not cause social distress or impairment and is sanctioned and monitored by a clinician. While persons who medically use prescription opioid analgesia do experience physical dependence and tolerance (decreased effect to the same dose repeated over time) as a result of physiologic changes on neuronal surfaces, they do not display maladaptive symptoms of opioid use disorder (OUD) such as desire to reduce use,

use of higher amounts than originally intended, or changes in recreational activities in order to engage in repeated use. Because they do not display these pathognomonic signs of addiction, persons prescribed opioid analgesia for treatment of pain in a monitored clinic setting are not considered to have OUD, according to the Diagnostic and Statistical Manual of Mental Disorders – Version 5 (DSM-5).[1]

Opioid use disorder (OUD) is maladaptive use of prescription opioids or illicit opioids, such as heroin. Unlike persons taking opioids under a prescriber's supervision (see above), persons with OUD are likely to frequently take more medication than they are prescribed, take medication prescribed to somebody else, perseverate on obtaining the next dose of medication, and suffer social consequences resulting from their substance use.

OUD is a type of s*ubstance use disorder* (SUD). SUD, for the purposes of this report, is an "umbrella" term that can refer to maladaptive use of any one, or more than one, drugs of abuse, including alcohol, illicit or illicitly obtained prescription opioids, anxiolytic, hypnotic, or sedative drugs. Aligning with the variability in terms for OUD used in the medical literature, many of which will be reviewed here, the terms *addiction* is used interchangeably with SUD or OUD in this Opinion.

Polysubstance use disorder (PUD), also a type of SUD that often overlaps with OUD, refers to the concomitant maladaptive use of more than one drug including alcohol, illicit or illicitly obtained prescription opioids, anxiolytic, hypnotic, or sedative drugs.

Opioid misuse refers to opioid analgesia use outside of the dose and frequency prescribed by a supervising clinician. For instance, a patient prescribed opioid analgesia for back pain who took one extra pill for breakthrough pain would be considered to have misused prescription

opioids. Opioid misuse is not the same as NMPOU, where the purpose of ingesting the drug is outside of the purpose for which it was prescribed (the latter usually being pain).

Non-medical prescription opioid use (NMPOU) is part of OUD, but not all NMPOU represents OUD. People with OUD engage in NMPOU chronically and maladaptively, suffer consequences from their NMPOU but cannot alter their behavior as a result of those consequences, and experience social distress as a result of their NMPOU.

II. Key epidemiologic concepts

Here I present some selected key epidemiologic concepts that are central to discussion about the nature and causation of any epidemic.

Epidemiology. A simple definition of epidemiology, also called population science, is the study of causes of disease in human populations. The role of an epidemiologist's opinion in the context of this litigation is to evaluate the soundness of the contention that prescription of opioid analgesia by a provider and dispensing of that medication through a licensed pharmacy, to persons apparently seeking treatment for pain, has caused an epidemic of non-medical use of prescription opioids obtained mostly illicitly plus use of illicit opioids.

Sensitivity. Sensitivity refers to the proportion of people with a disease of interest who are labelled as positive for the disease by a diagnostic test or case definition.[2] To mitigate adverse consequences of a disease of interest, discovery of as many afflicted persons for inclusion in the intervention cohort as possible – in other words, having a highly sensitive algorithm for identifying cases - optimizes the efficacy of that intervention.

Specificity. Specificity refers to the proportion of people without a disease who are labelled as negative for the disease by a case definition.[2] Inclusion of "false positive" cases – that is,

persons who do not have the disease of interest but are labelled as positive for it – in a study cohort attenuates the power to identify an association between an intervention and reduction in adverse outcomes.

Population at risk. Defining a population at risk for study or intervention requires eligibility criteria that are both sensitive and specific, if one aims to accurately quantify the impact of the intervention under investigation. *Inclusion criteria* refers to characteristics of afflicted people who would receive the intervention. Carefully delineated *exclusion criteria* limit the possibility of inclusion of false-positive cases in an intervention cohort, and thus reduce the likelihood that an effective intervention is not identified as such due to dilution of its effect.[2]

Incidence (sometimes called *incidence proportion*). Incidence refers to the proportion of subjects developing a disease *de novo* from among all subjects followed during the study's time period. As incidence is one way to report disease *onset*, by definition, all subjects are without the disease at the beginning of the study time period.[2] If one were interested in quantifying the incidence of a particular disease in a population of patients, patients with the disease present at baseline would be identified and excluded from the "at risk" population at the beginning of the follow-up period.

Prevalence (sometimes called *prevalence proportion*). In contrast to incidence, prevalence refers to the proportion of people in a population who have a disease at a given moment in time. Prevalence is affected by both incidence, which refers to the rate at which *de novo* disease arises, and the duration of the disease.[2] Prevalence is not informative as to when or how each person in the numerator developed the disease under study.

Incidence, prevalence, and causality. In his classic text *Epidemiology: An Introduction*, Kenneth Rothman states "Because prevalence reflects both incidence rate and disease duration, it is not as useful as incidence alone for studying the causes of disease." Because many diseases studied are common in the general population, simply measuring prevalence of a disease in any population with an exposure of interest will yield a result that is uninterpretable from a causal point of view. As an illustrative example, the National Survey on Drug Use and Health (NSDUH) estimates that 7.2% of the US population abused alcohol or illicit substances, the latter including marijuana, prescription opioids, cocaine, methamphetamines, heroin, and stimulants.[3] Therefore, on average, 7.2% of persons walking into a grocery store suffer from an SUD. However, it would not be reasonable to interpret that this proportion indicates that shopping for groceries *causes* SUD.

Confounding. Confounding is a confusion of effects, such that the effect of one exposure, when measured, is mixed with the effect of another variable that is impacting an outcome of interest. In order for a variable to be considered a *confounder*, it must be closely associated with both an exposure of interest and the outcome (such as the new diagnosis of a disease).[2] One strategy to mitigate confounding is restriction of the inclusion cohort to eradicate the effect of the confounding variable, so any apparent causal relation between the exposure and the outcome is more likely to be a true one.[2] An example of confounding is that in a researcher might wish to isolate and quantify the association between neonatal abstinence syndrome and learning disabilities. However, the analysis would have to account for the potential confounder of concomitant alcohol use in mothers of babies with NAS, as maternal alcohol use has also been associated with learning disabilities in children. In observational studies, restriction of the

inclusion cohort (in this case, to children of mothers who only ingested opioids and used no alcohol during pregnancy) is often not feasible, with the proportion of mothers abusing opioids but not alcohol too small to demonstrate statistically significant, isolated effect of NAS on learning disabilities.

IV. Methodology, including literature search and types and quality of studies reviewed

As a population scientist, I undertook a review of the peer-reviewed medical literature in an effort to quantify answers to the following questions:

● What is the incidence of OUD in the population of people prescribed opioids for pain in a controlled clinical setting (ie not a "pill mill," through a street dealer, etc)? What is the incidence of opioid overdose or opioid-related death in this population, and how is that changing over time?

● Is the population of patients who engage in NMPOU as part of their opioid addiction the same population as those who are prescribed stable doses of opioids for pain?

● From where do people who engage in NMPOU obtain their opioids?

● What is the incidence of heroin initiation in persons prescribed opioid analgesia for pain in a controlled clinical setting? Does prescribing opioids in stable doses in a monitored clinical setting cause heroin use?

● What are the pathophysiologic changes in the brain that cause addiction? Would these changes occur in the absence of access to one of the substances to which the addicted brain responds, or does the underlying pathophysiology manifest itself regardless of the drug environment?

● Which population is targeted by efforts so far to mitigate the opioid crisis?

What has been the impact of these interventions?

To answer these questions, I searched the peer-reviewed medical literature for terms pertinent to the topics above. I scanned returned titles for studies that may have been informative in relation to the questions of interest, and if abstract review confirmed relevance of the study, I downloaded the full text for closer review. Full text was available for all studies selected by subscription through my faculty appointment at Harvard Medical School, and most of these would available to the public. I scanned references in articles found during the initial Pubmed search for additional pertinent articles. I favored studies reporting results using original data over reviews of citing data originally published elsewhere; if a review by one author cited data from another published paper, I retrieved the original paper and reviewed and cited findings from that. In addition, I reviewed data from publicly maintained websites related to prevalence of OUD and opioid-related deaths where appropriate, including the Substance Abuse and Mental Health Service Administration (SAMHSA), Centers for Disease Control (CDC), and National Institute of Drug Abuse (NIDA) websites. I retain the right to amend the list of studies considered should additional evidence related to these topics become available.

In reviewing each study, I focused on the methods in order to gain a clear understanding of which outcomes the study purported to report, and which population was sampled to quantify that outcome. I scanned methods sections for inclusion/exclusion criteria for the sampled population. For each study, I reviewed the sample's baseline characteristics to determine whether any reported proportions were prevalences or incidences (i.e., more likely to be indicative of a causal relationship), and for confounders that could impact the

interpretation of the study's findings. If I discovered confounders among the characteristics of the sampled population, I studied the analysis sections determine whether the presented results accounted for these or not.

V. Opinions

Based on my review of the literature and on my prior experience as a clinician and epidemiologist, I have reached the following conclusions.

1. While there is small amount of overlap, patients with acute, chronic, and/or cancer pain who are prescribed stable doses of opioid analgesia in a supervised clinical setting represent a separate population than patients who use illicit opioids or illicitly use prescription opioids.
2. Most patients who are prescribed stable doses in a supervised clinical setting do not develop OUD.
3. Guideline-sanctioned use of opioid analgesia for chronic or cancer pain entails use of short-acting formulations that require dosing 3 or 4 times daily, even when the overall daily dose is less than 50 morphine equivalents (MEQ).
4. There is no evidence that treatment of patients with pain with stable doses of opioid analgesia has a direct causal relationship with use of heroin.
5. In contrast to people taking opioids in a clinically monitored, stably-dosed fashion, people with OUD have a disease of the brain, with genetic as well as environment influences. OUD, like any SUD, is often accompanied by other diseases of the brain such as debilitating psychiatric diseases.

6. SUDs and other psychiatric diseases are prevalent in human populations, and SUD is therefore measurable in countries around the world, regardless of which substances and in what quantity, are accessible in those countries.
7. The disrupted brain circuitry in addiction is non-discriminating, and therefore persons with OUD often have a history of maladaptive use of ≥ 1 other substance of abuse.
8. Most people with OUD who abuse prescription opioids do not obtain them directly from a doctor. They steal them or are given them by friends or family, or buy them from a dealer.
9. Because people with OUD are prone to abuse of any substance, in people with OUD who use heroin, sometimes heroin initiation precedes, and sometimes it follows NMPOU.
10. Now, most opioid-related overdoses and deaths are in people with OUD who are using illicit opioids. The majority of opioid-related deaths are caused by heroin and related illicit opioids, with a growing proportion of those caused by fentanyl.
11. Of opioid-related deaths in people who had used prescription opioids, most involved another concomitant substance such as a benzodiazepine.
12. People with OUD are under-engaged for rehabilitation and treatment of their disease. They are not prevalently represented in the more easily capturable population of persons receiving monitored stable doses of opioids for chronic pain. Resources are out-matched by the number of persons requiring treatment, and treatment facilities that are available do not always use proven effective therapies for OUD, especially Medically Assisted Treatment (MAT).

13. Efforts to mitigate the opioid crisis, such as state-level Prescription Drug Monitoring Programs (PDMPs), have been associated with decreases in the supply of opioids, mostly to people on monitored stable doses of opioids for pain. Because such efforts do not target persons with OUD, who for the most part do not obtain opioids from such settings, these efforts have had minimal impact on opioid-related death rates.

VI. Evidence upon which my opinions are based

1. Persons who are prescribe opioid analgesia for pain at stable doses represent a separate population than persons with OUD, many of whom abuse multiple substances and most of whom obtain abused prescriptions from outside the controlled clinical context when they engage in NMPOU.

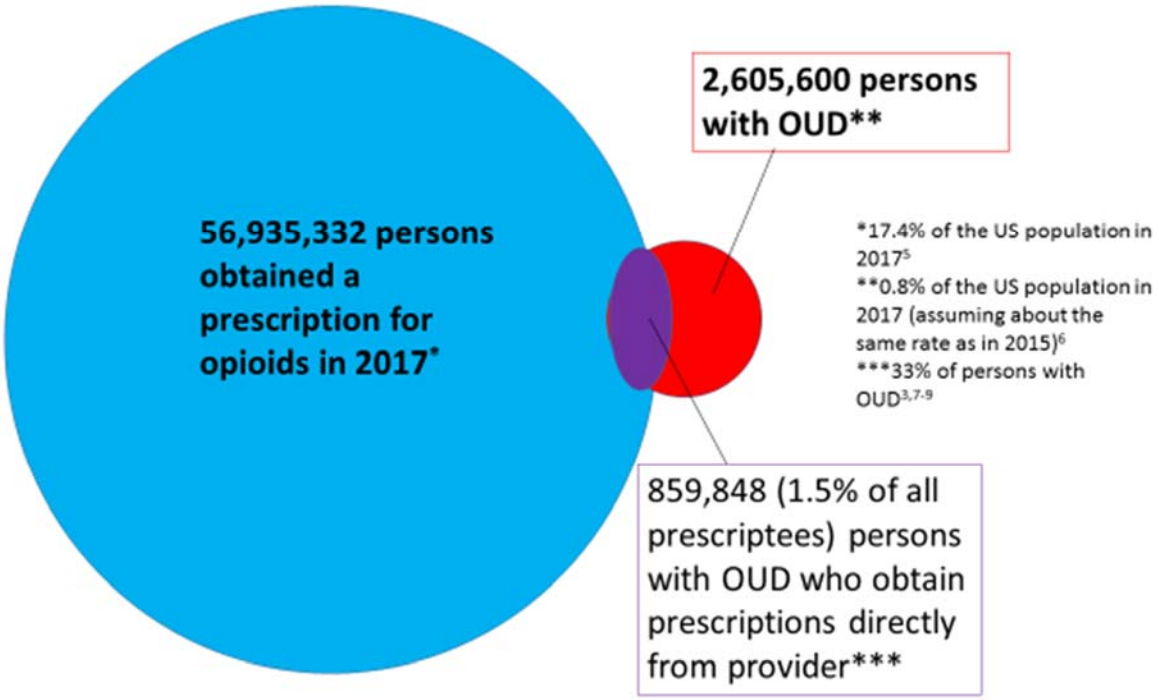

Figure 1. Persons prescribed opioids for pain, and persons who have OUD.

Persons prescribed opioids for pain and persons who have OUD represent two disparate populations, with some but not total overlap. Using data reported by IQVIA, which collects dispensing information directly from retail pharmacies and long-term care facilities,[4] the Centers for Disease Control (CDC)[5] reports that in 2017, 56,935,332 persons, or 17.4% of the U.S. population, received one or more prescriptions for opioid analgesia written by a healthcare provider (blue circle in Figure 1). Han et al[6] report that 1.9 million persons in the US had an OUD, which represents 0.6% (1.9 million divided by US population of 321 million in 2015); however, they also report the discrepant statistic of 0.8% of the US population as having OUD. Erring on the side of the worst-case scenario and assuming that 0.8% of the 2017 US population had an OUD, we can estimate that 2,605,600 persons had an OUD in 2017. Studies examining sources of abused prescription opioids in persons who engage in NMPOU, including those with OUD, have determined that between 62 and 76% obtain their abused prescription opioids through some source *other than their own prescriber*.[3,7-9] Therefore, if we estimate that approximately a third (part-way between 62 and 76%) of people with OUD are supplied their abused opioids by their prescriber (purple ellipse in Figure 1), 33% of the 2,605,600 persons with OUD, or 859,848 persons with OUD, were prescriptees of opioids through licit channels. So among the 56,935,332 opioid prescriptees in 2017, 859,858 (1.5%) abused their opioid prescriptions in the context of an OUD, while the other 98.5% used their opioid analgesia for treatment of pain. Sources of prescription opioids used by person with OUD are discussed in more detail below.

2. Among persons prescribed opioid analgesia for acute, chronic, or cancer pain, a minority engage in NMPOU of those prescriptions, and a minority develop de novo OUD.

Many authors have examined the prevalence of OUD in populations of patients prescribed opioid analgesia by a provider in a controlled clinical setting. Vowles et al[10] reviewed 38 studies to calculate the prevalence of 3 types of problematic use among patients prescribed opioids for pain: misuse, in which the opioid is used "…contrary to the directed or prescribed pattern of use"; abuse, in which the subject intentionally uses the opioid for non-medical purpose such as euphoria; and addiction, characterized by repeated use despite demonstrated harm from that use, with impaired control over that use. These authors' definition of addiction aligns with the definition of OUD as defined above and used throughout this report. The authors assessed study quality by examining whether the cohort was consecutively sampled or was a random subset; what proportion of data was missing/had to be imputed; whether methods were adequately described (i.e., if "problematic behavior" as the outcome was clearly defined); and whether raters of problematic use were blinded. Because they determined that the included studies varied in quality and in the size of the cohort, they weighted prevalence for each study accordingly in calculating ranges of estimates. Rates of addiction (or OUD) averaged between 8 and 12% with a 95% confidence interval (CI) of 3% to 17%. Abuse was reported in only one study and had a prevalence of 8%. The authors examined whether variation in study methodology impacted results, and found that prevalence of addiction was generally lower in studies that had addiction as the primary, as opposed the secondary, objective of the study. In other words, studies designed primarily to determine

prevalence of OUD among patients prescribed opioids for pain reported lower prevalence proportions than studies designed to assess some other outcome.

Prevalence of OUD reported by Vowles et al is cited as support for OUD "following" medical use of prescription opioids by expert witnesses for the Plaintiffs.* However, prevalence of any disease represents a moment in time and is incorrectly conceptualized as "following," and therefore caused by, any exposure or condition. As discussed above, prevalence is impacted both by the incidence of a disease in the population and the duration of the disease following its onset. Conclusions regarding causality between opioid analgesia prescribed for pain, and *de novo* OUD, are better derived from studies reporting the incidence of OUD among all patients prescribed opioids for pain. Higgins et al[11] reviewed 12 reports describing new opioid dependence or abuse disorder, among patients with pain in receipt of opioid analgesia treatment. Opioid abuse or dependence, which for the purposes of this Opinion can be considered as synonymous with OUD, was defined by DSM-IV or International Classification of Disease-Ninth Revision (ICD-9) codes criteria, or by clinician assessment in each of the studies included in the meta-analysis. Studies that reported existing cases (that is, prevalence) were excluded. Study quality was rated as "poor," "fair," or "good," using risk of bias tools designed by the National Institutes of Health;[12] only studies of fair or good quality were included. The random effects model, accounting for both within-study and between-study variance, was used to generate incidence. Because there was one included study that had an event rate (that is, incidence rate) of 0, a "continuity correction" was applied in which a constant value was added

* *Throughout this report I use the term Plaintiffs' expert witnesses to denote witnesses designated by the Plaintiffs as proposed experts on these issues; in using this term I do not intend to endorse these witnesses' qualifications to offer opinions as experts.

to each of the cells in the contingency table, allowing the 0-count study to contribute to the pooled estimate. The authors found a pooled incidence of opioid dependence or abuse of 4.7% (95% CI, 2.1-10.4%). In sensitivity analyses, they found that estimates of incidence were lower (3.1%) when only studies of "good" quality were included in the meta-analysis, and higher (15.1%) when only studies of "fair" quality were included. Pooled incidence of opioid dependence or abuse also varied by diagnostic criteria for identifying dependence or abuse (DSM vs ICD-9 criteria), with the pooled incidence among studies using ICD-9 codes to capture abuse or dependence reported as 1.3%, while studies using DSM criteria generated a pooled incidence of 11.3%. While the risk of developing OUD among persons prescribed opioids for pain is not 0, it is a small minority of persons with pain treated with opioid analgesics who developed OUD. Persons with OUD mostly represent a separate population.

3. Current guidelines for treating people with chronic non-cancer pain recommend more daily doses of short-acting formulations, as opposed to fewer daily doses of long-acting formulations.

All medications, including those for treatment of pain, carry risks for adverse effects, including death for some medications. For opioid analgesic medications, there is some risk of death caused by an adverse event related to the medication, which is comparable to that of non-opioid analgesics. Solomon et al[13] compared Medicare beneficiaries treated with opioid medications for arthritic pain to propensity-score matched beneficiaries prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and found a similar rate of adverse-event-related deaths (12 per 1000 person-years in the opioid group versus 13 per 1000 person-years in the NSAID group). An expert witness for the Plaintiffs* instead offers the rate of all-cause

mortalities in these two groups, a difference that cannot be definitively be attributed to the use of opioids compared to NSAIDs given that the cause-specific mortality is the same between the two groups. The propensity scoring may not have perfectly matched the two groups and some other confounding difference in morbidity between those prescribed NSAIDs and those prescribed opioids for pain may underlie the difference in all-cause mortality. Risk for fatal and non-fatal overdoses in patients prescribed opioid analgesia varies in accordance with well-studied risk factors including concomitant benzodiazepine use, and higher dose of opioid medications. Current guidelines for treatment of persons with chronic pain advise prescribers to be mindful of these risk factors and prescribe accordingly.[16-17] For instance, Dunn et al[14] studied 9,940 patients newly prescribed opioids for chronic pain and followed for a mean of 42 months. Fifty-one of the patients (0.5%) suffered an opioid overdose; because patients with a history of SUD were not excluded from the cohort, 6 of these overdoses were in patients not prescribed any opioid medication (a control group). Gomes et al[15] identified 1,463 opioid-related deaths among 607,156 (0.2%) people receiving ≥1 opioid prescription paid for by the Ontario public drug plan. While the *overall* overdose and opioid-related death rates were small, they were dose-dependent, with patients receiving 50 to 99 milligrams (mg) daily having a 3.7-fold increase in risk for overdose compared to persons receiving 1 to 20 milligrams daily (Dunn et al); and patients receiving >200 MEQs daily had nearly a 3-fold increase in risk for opioid-related death compared to low daily doses of <20 MEQs (Gomes et al). While the risk of overdose and opioid-related deaths were dose dependent, the overall rate of overdoses and deaths in both these cohorts was small (0.5% and 0.2%, respectively). Because of this small, but dose-dependent risk of opioid overdose and death in patients with pain prescribed opioid

analgesia in a monitored clinical setting, guidelines issued by the CDC,[16] Veterans Affairs/Department of Defense (VA/DoD),[17] and others recommend non-pharmacologic and non-opioid pharmacologic treatment for chronic pain as a "first line," with opioid analgesia added in parallel when initial interventions are not effective by themselves and after a risk/benefit conversation with the patient has taken place. When opioid analgesia is prescribed, especially by providers who are not pain specialists, current guidelines recommend low total daily doses of ≤50 MEQ.

There is some evidence that prevalence of OUD among people with pain prescribed opioid analgesia increases incrementally with ≥90 days of treatment. Edlund et al[18] studied 568,640 subjects with chronic pain in the Healthcore Integrated Research Database, 197,419 of whom were prescribed opioid analgesia. There were 497 post-index diagnoses of opioid abuse or dependence (that is, OUD), with 347of these in the 197,419 prescribed opioid analgesia. Patients who were prescribed opioids for ≥90 days had a risk of OUD that was many-fold higher than those prescribed <90 days. The Edlund study is cited by expert witnesses for the Plaintiffs* as evidence of the association between the prescription of opioid analgesia and the development of OUD; however, again this study cites prevalence, not incidence, and a low prevalence (347/197,419=0.2%) at that. Because OUD was more prevalent in persons prescribed opioid analgesia for ≥90 than in persons prescribed for <90 days, the VA/DoD guideline strongly advises against treatment with opioid analgesia for a period longer than 90 days.[17]

There is some evidence that long-acting opioid formulations carry a greater risk for overdose than short-acting formulations. Miller et al[19] studied 840,729 veterans with chronic

pain prescribed short-acting opioids in the national VA pharmacoepidemiology database, of whom 319 (0.04%) suffered an unintentional opioid overdose. The overall incidence of the outcome was small, but differed according to whether the patient was prescribed long-acting versus short-acting opioids, with those prescribed long-acting opioids having 2.33-fold higher risk for overdose when compared to prescriptees with short-acting opioids. Because of this, the CDC guideline[16] recommends short-acting formulations instead of long-acting formulations.

To summarize, current guidelines for use of opioid analgesia in treating patients with chronic pain generally advised non-opioid interventions as first-line treatment. When opioid therapy is prescribed, the guidelines recommend low doses (<50 MEQ) of short-acting formulations for durations that are ideally not longer than 90 days, out of an abundance of caution (again, prevalence and incidence of OUD, opioid overdose, and opioid-related death among opioid prescriptees in monitored clinical settings is low, see above). The table below reports durations of action and dosing schedules for commonly prescribed short-acting opioids.[20]

Generic Name	**Trade Name**	**Duration of activity**	**Usual adult oral dose and schedule**
Hydromorphone	Dilaudid	4-5 hours	2 mg every 4 to 6 hours
Morphine sulfate	Roxanol	4-5 hours	10 to 30 mg every 4 to 6 hours
Oxycodone	Percocet	3-6 hours	5 to 10 mg every 4 to 6 hours
Hydrocodone	Vicodin	4-5 hours	5 to 10 mg every 4 to 6 hours
Codeine	Codeine	4-6 hours	15 to 60 mg every 4 hours

Derived from Mosby's Medical Drug Reference Edition 6[20]

An average patient with chronic pain for which he is prescribed opioid analgesia within the constraints of the guidelines might consume between 6 and 12 tablets daily for 90 days (between 540 and 1080 tablets within a calendar year). The CDC reported that the prevalence of chronic pain in the US was 20.4% in 2016.[21] If 20.4% of Summit County, Ohio's adults had chronic pain, and 20% to 30% of these were prescribed "acute" (<90 days) opioid analgesia within parameters of current conservative guidelines, that legitimate medical use would account for approximately 18,744,693 to 28,117,040 doses of opioids utilized in Summit county in 2016. Using the same assumptions for prevalence of chronic pain and proportion treated for some time with opioid analgesia, and applying these to the population of Cuyahoga County in 2016, legitimate medical use could account for 43,584,848 to 65,377,272 pills delivered to the county that year. Given that this estimate of opioid doses for within-guideline treatment of chronic pain in a monitored clinical setting does not include patients treated chronically (≥90 days) or for cancer or acute (trauma, post-surgery) pain and that 20.4% might be a conservative estimate for the prevalence of chronic pain in Summit County, there is no foundation for suggesting that the number of opioid dosage units going into the county, standing alone, should have raised concerns that large amounts of opioid medications were being diverted. It also assumes that the prevalence of chronic pain in 2016 was not higher than that in the country at large, which may have been the case. Paragraph 690 of the Summit County's Third Amended Complaint contends that isolated consideration of the annual average of 36,400,000 opioid pills dispensed in Summit County per year between 2010 and 2016 should have been an indication that many such pills were being diverted. However, given that current guidelines recommend short acting doses, allow for dosing up to 50 MEQs daily, and allow for dosing up to

90 days, the number of pills dispensed in this location in this time frame is not substantially different from what would be expected if all of the pills were prescribed by a physician and used in accordance with that prescriber's instructions by people with clinical indication for them (i.e., pain).

4. The medical literature does not support the contention that prescribing opioids for pain results in initiation of heroin use.

My research identified no studies that examined incident heroin initiation among patients with pain who are prescribed opioid analgesia. Findings reported in selected studies cited by the Plaintiffs' expert witnesses* as support for an association between opioid analgesia and heroin use, are tabulated below. Three of these studies reported incidence of heroin and/or injection drug initiation among persons engaged in NMPOU;[22,23,24] three reported prevalence of prior NMPOU in heroin users;[25,26,27] one reported prevalence of heroin use in persons engaged in current NMPOU;[28] two reported prevalence of NMPOU in intravenous drug users;[29,30] one reported use prevalence of OxyContin use in persons with OUD;[31] and two reported qualitative findings only.[32,33] All of these studies enrolled adults with pre-existing NMPOU or abuse of illicit heroin. None of them support the "Gateway" hypothesis, which suggests that persons prescribed opioid analgesia become addicted to it, have their supply of abused opioids discontinued by their prescriber, and turn to heroin, purchased on the street, to maintain their addiction. In order to address such a hypothesis, one would have to start with a denominator of persons without a history of OUD (including no prior heroin abuse) who prescribed opioid medication for pain in a controlled clinical setting, and then follow that

cohort prospectively for *de novo* heroin abuse. None of the studies abstracted here have such an approach described in their methods.

First author	Year	Sampled Population (Denominator)	Reported Proportion (Numerator)
Grau LE[22]	2007	Persons engaged in NMPOU	Incidence of heroin initiation
Muhuri PK[23]	2013	Persons engaged in NMPOU	Incidence of heroin initiation
Banerjee G[24]	2016	Veterans with and without NMPOU	Incidence of heroin initiation
Lankaneau SE[29]	2012	Persons engaged in injection opioid use (not exclusively heroin)	Incidence of prescription opioid misuse
Khosla N[30]	2011	Current and former intravenous drug users	Prevalence of current NMPOU
Jones CM[28]	2013	Persons engaged in NMPOU	Prevalence of heroin abuse
Cicero TJ[31]	2015	Patients meeting DSM criteria for OUD	Prevalence of OxyContin abuse
Cicero TJ[25]	2014	Patients meeting DSM criteria for heroin use/dependence	Prevalence reporting prescription opioids prior to heroin use
Siegel HA[26]	2003	Recently initiated heroin users	Prevalence reporting prescription opioids prior to heroin use
Pollini RA[27]	2011	Young heroin injectors	Prevalence reporting prescription opioids prior to heroin use
Mateu-Gelabert P[32]	2015	Persons engaged in NMPOU	Qualitative results only reported
Mars SG[33]	2014	Heroin injectors	Qualitative results only reported

5. Unlike most people prescribed stable doses of opioids for pain, people with SUDs suffer from a disease of the brain, with genetic as well as environmental influences, and often with accompanying debilitating psychiatric disease.

Figure 2 describes the brain disease model of addiction.[34] Neuroanatomically, drug-induced activation of the brain's reward centers (thalamus, globus pallidus, dorsal striatum – see Figure 2) is enhanced by conditioned cues from other areas of the brain (hippocampus, anterior cingulate cortex, orbitofrontal cortex), which have been sensitized by repeated exposure to a psychotropic substance. When the substance is withdrawn from the pre-conditioned, addicted brain, activation of brain regions involved in emotion (ventral striatum,

amygdala, basal nucleus) results in negative mood and maladaptive response to stress. This leads to life-disrupting pre-occupation with obtaining the substance again, overpowering the brain's built-in capacity to abstain from the drug (pre-frontal cortex). Biochemically, SUD is the manifestation of disruptions in the dopamine and glutamate systems in the brain. In the brain disease model of addiction, the affected person moves from binge consumption and intoxication, to withdrawal when the substance becomes unavailable, and finally to pre-occupation with obtaining the next bolus of the substance.

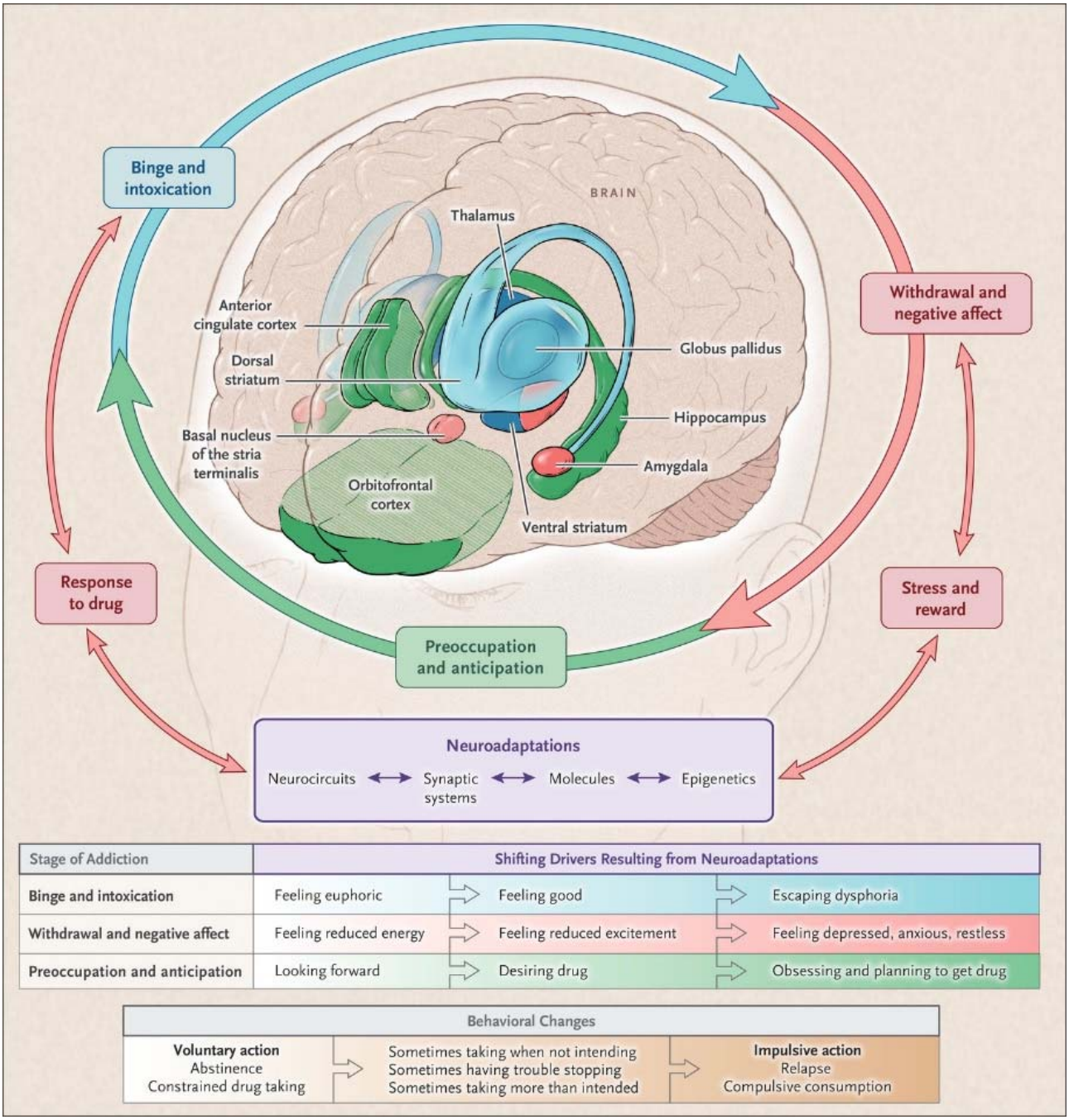

Figure 2. The brain disease model of addiction.[34]

The brain disease model of addiction is supported by studies demonstrating that administration of addictive drugs (any of them) result in sharp increases in dopamine in reward regions of the brain in animal models.[35] Neuroplasticity resulting from episodic drug-induced surges of dopamine that attenuate over time underlie transition from binge use to chronic daily

use (SUD), and are supported in animal models of addiction.[36-39] Adaptations in the circuitry of the amygdala and basal forebrain are associated with a person's increased reactivity to stress and increase in negative emotions, demonstrated by studies in rats and humans examining the roles of these brain structures in phasic versus sustained fear.[40] Brain imaging studies in humans have demonstrated that in the addicted brain, down-regulated dopamine signaling not only dull the reward center's sensitivity to pleasure, but impair executive processes including for self-regulation, including the will to abstain from using substances.[41] Because the pathophysiology underlying SUD is present in minority of the population, Dr. Nora Volkow, Director of the National Institute on Drug Abuse, writes "…[OUD] will occur in only a small percentage of patients exposed to opioids. …once [SUD] develops, it is a separate, often chronic medical illness that will typically not remit simply with opioid discontinuation and will carry a high risk of relapse for years without proper treatment."[42]

Like most medical illnesses, SUD has environmental and genetic contributors. Harrington et al[43] used data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to examine various risk factors for incident drug use in adults. NESARC was a longitudinal study, with 2 waves of survey; the cohort included for this analysis was restricted to those who reported abstention from any drug use during Wave 1 of surveys were included. Incident SUD as determined during Wave 2 of the survey was found to be associated with childhood adversity (physical abuse, witnessed fights at home, neglect, sexual assault), family history of SUD, age (older age categories had decreased risk for SUD compared to the youngest subjects, aged 18 to 29), sex (higher risk in males), race (Hispanic and Asian/Hawaiian subjects at lower risk than white, black, American Indian subjects), and marital status (widowed

or never married subjects were at higher risk). Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in genes involved in cellular manufacture of calcium and potassium signaling pathways.[44] At least 20% of variance in vulnerability to SUD is attributable to several common SNPs identified through GWAs.[45] Copy number variations (CNV), which are another type of genetic mutation, have be associated with OUD in particular.[46] While one could conduct a more comprehensive review of all the studies that have identified specific genetic mutations that are associated with vulnerability to SUD and OUD, these few studies are enough to support the contention that persons with SUD have genetic influences that underlie their disease.

Because persons with SUD have dysfunctional neuroanatomy and neurochemistry, other psychiatric diseases are common comorbidities in this population, and many pre-existing psychiatric diagnoses are risk factors for developing SUD. In cross-sectional data obtained from the NSDUH, 2002-2004, Becker et al found that persons with opioid abuse/dependence were more likely to have panic and social phobic/agoraphobia symptoms.[47] Katz et al[48] used information on mood, personality, and substance use disorders collected during Wave 1 of NESARC to examine the relation between these and opioid use/dependence identified during Wave 2 of data collection. Axis I disease (such as depression or schizophrenia) and Axis II (personality disorders) were associated with odds ratios (95% CI) of 3.29 (1.48-7.32) and 4.60 (2.38-8.90), respectively, with subjects with both Axis I and II disorders having an OR for Wave 2 opioid use/dependence of 8.16 (4.44-14.99). Using NESARC data, Wu et al[49] found a prevalence of SUD (including cannabis, alcohol, nicotine, cocaine, opioid/heroin, sedatives, or polysubstance) of 13.5% in 13 to 17 year olds who were diagnosed with a psychiatric disease

(included anxiety, mood, conduct, attention deficit/hyperactivity, personality, adjustment, eating, impulse-control, psychotic, learning, mental retardation, and relational disorders).

6. SUDs, like other diseases, are prevalent in human populations, and SUD is therefore measurable in countries around the world, regardless of which substances and in what quantity are accessible in each country.

The Global Burden of Disease study,[50] an endeavor of the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, is the most comprehensive effort internationally to measure trends in disease prevalence in countries around the world. Staff at IHME collaborate with researchers in reporting countries to quantify the impact (i.e. death rates) of hundreds of diseases and injuries, and risk factors for these, on an annual basis. In Figures 3a, 3b, and 3c, below, deaths from cocaine use disorder, amphetamine use disorder, and OUD are reported for the years 1990 to 2016, respectively. These figures demonstrate that deaths for cocaine and amphetamine use disorders have increased dramatically in the US, as have deaths due to OUD. In this light, the "opioid crisis" appears more like a substance abuse crisis in general, in which persons with addiction, regardless of their abused substance of choice, are being under-captured and treated for their diseases.

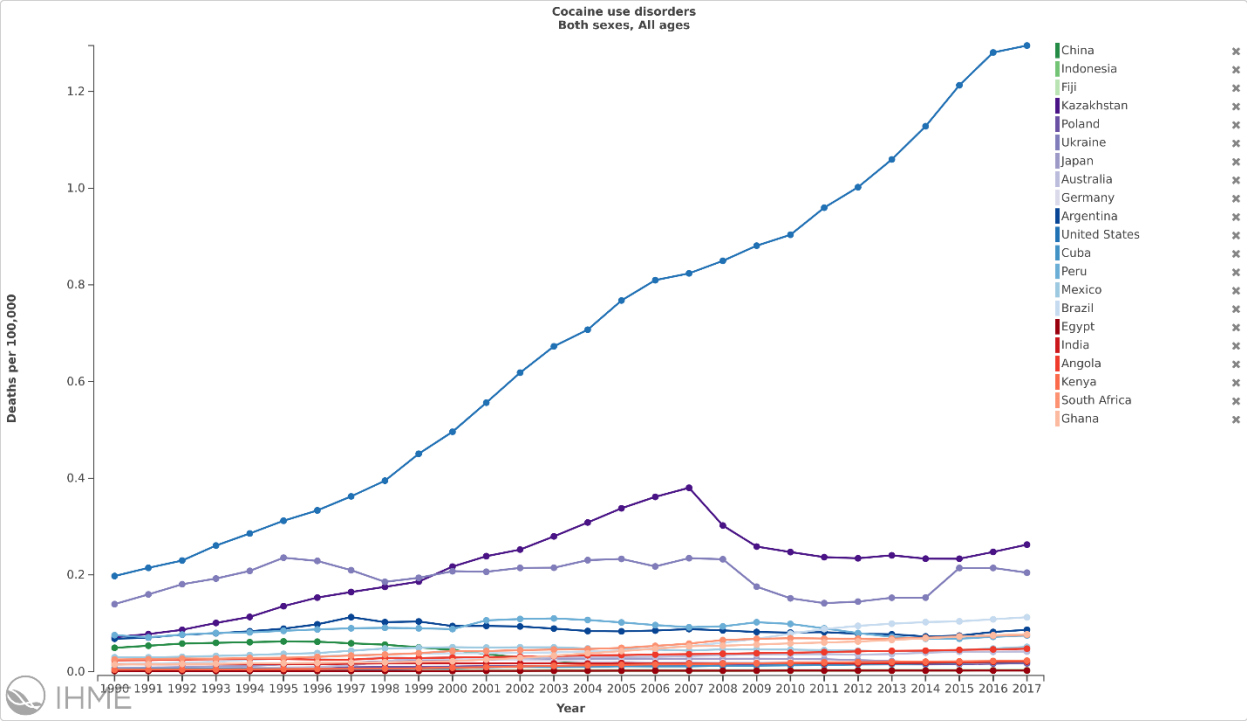

Figure 3a. Deaths from cocaine use disorder, by country and by year.[50]

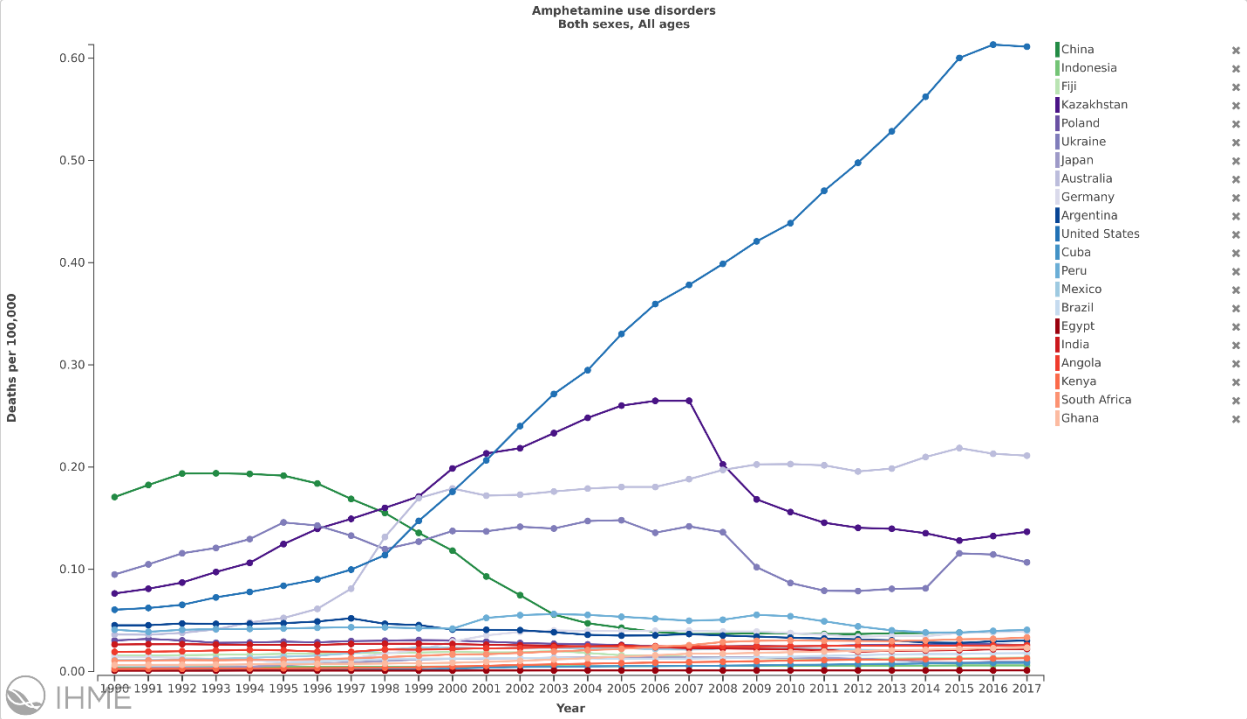

Figure 3b. Deaths from amphetamine use disorder, by country and by year.[50]

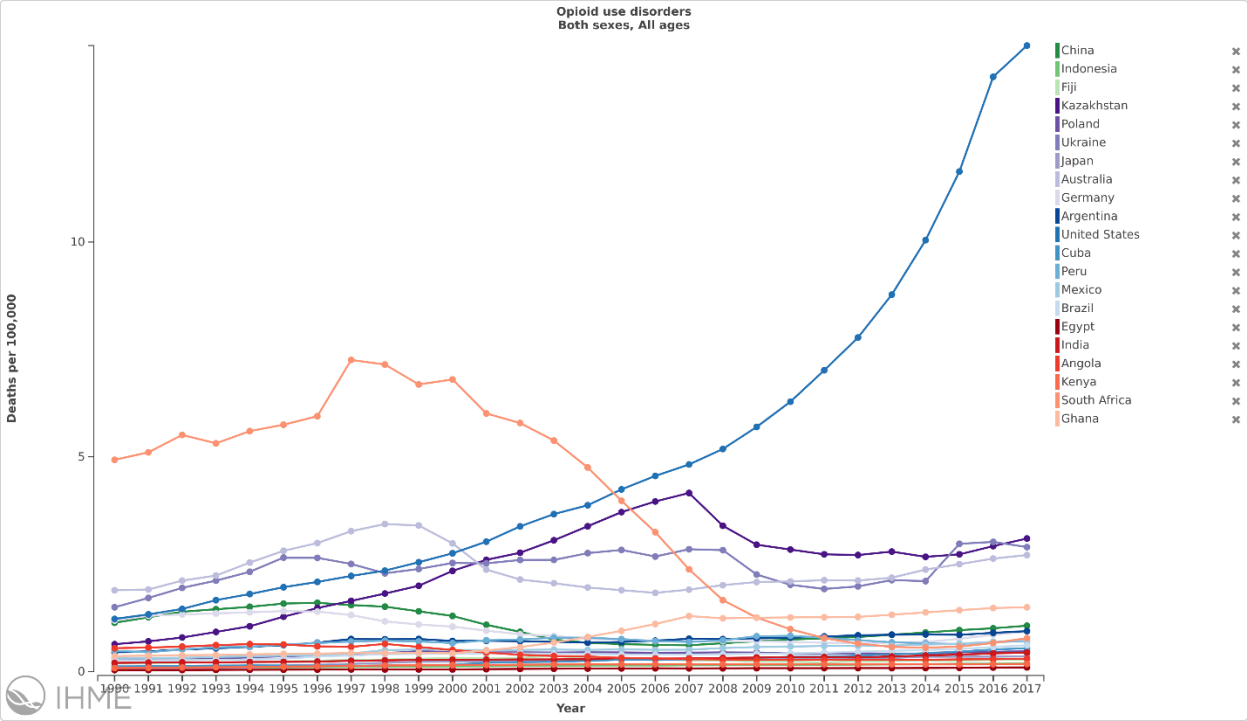

Figure 3c. Deaths from OUD, by country and year.[45]

7. In persons with SUD, disrupted brain circuitry does not discriminate between different drugs of abuse. Therefore, persons with SUD often have a history of PUD, confounding studies attempting to quantify the relationship between isolated NMPOU and OUD.

Many of the SNPs identified as associated with SUDs including cannabis, alcohol, and illicit drugs such as cocaine or heroin, have been identified both in persons with one type of SUD (for instance, alcohol dependence) and in other persons with another type of SUD (for instance, cocaine).[45] These varied genetic mutations manifest phenotypically the same way: disordered reward, emotional, and stress-control brain circuits. Therefore, persons with SUD often engage in maladaptive use of multiple substances (PUD). Numerous studies have demonstrated that persons with OUD abuse one or more non-opioid substances, before, during

or after their abuse of prescription or illicit opioids; a sample of them are summarized here. Muhuri et al[23] found that while 80% of recent heroin initiates reported NMPOU prior to initiating heroin, between 77 and 86% (depending on the year of NSDUH data examined) of these reported prior polysubstance use including marijuana, cocaine/crack, hallucinogens, and/or inhalants. Muhuri's work is cited by expert witnesses for the Plaintiffs* as indicative of a causal relationship between NMPOU and heroin use because these heroin users reported NMPOU prior to heroin use; in actuality their analysis demonstrates that polysubstance abuse, not isolated NMPOU, frequently precedes heroin use. Winkelman et al[51] found that 83% of persons with OUD and 93% of persons who used heroin used ≥1 other drug (included sedatives/tranquilizers, stimulants, hallucinogens, or inhalants; NSDUH data was used for this study). The Survey of Key Informants Program (SKIP) study utilized Key Informants to recruit subjects with OUD who were entering substance abuse treatment through one of 125 privately and publically funded treatment centers participating in SKIP.[52] Cicero et al[52] found that 95% of persons seeking treatment for prescription opioid abuse reported use of other drugs including stimulants, benzodiazepines, or hallucinogens, prior to initiating use of opioids. In a cohort of 714 users of stimulants from nine rural counties in Arkansas, Kentucky, and Ohio, 380 (53.2%) began using opiates during the study period.[53] This study (Havens et al) is cited as one of 16 studies that one expert witness for the Plaintiffs* reports as evidence for the prescription opioid – heroin use link; however, the study focusses on NMPOU in users of stimulants as opposed to heroin use in persons engaged in NMPOU. Wall et al[54] used NSDUH data from 2013-2014 to examine generational differences in drug initiation sequences. Among other findings, these authors reported that most heroin users who engaged in NMPOU prior to

initiation of heroin had used cocaine between NMPOU and heroin use, or if heroin use followed in direct sequence after NMPOU, cocaine use had preceded the NMPOU. While the "Gateway" hypothesis advocates a linear NMPOU->heroin directionality in choice of substance abused among current heroin abusers, these studies support that heroin users most often 1) used multiple substances, that use including NMPOU, prior to initiating heroin; and that 2) underlying disrupted brain circuitry, which does not discriminate between different substances of abuse, underlies incidence and prevalence of heroin abuse, as opposed to some orderly exposure/access to one substance followed by the access to the next.

8. Most people with OUD who use prescription opioids do not obtain them directly from a doctor. They steal or are given the pills by friends or family, or they buy the pills from a dealer.

Studies examining sources of prescription opioids used by persons who engage in NMPOU, including those with OUD, have reported inconsistent results. According to NSDUH 2017 data,[3] about a third of persons who misuse prescription opioids obtain them directly from a health care provider through a prescription. The remaining 2/3s is obtained illicitly, with most misusers being given the pills from a family or friend and the remaining misusers obtaining pills through stealing or buying them. Thus, the majority of diversion of prescription opioids for NMPOU occurs after the medication is dispensed to the patient by a pharmacy, and therefore outside of the Drug Enforcement Administration's closed system.[59] Figure 4 is derived from findings reported in NSDUH 2017 results.

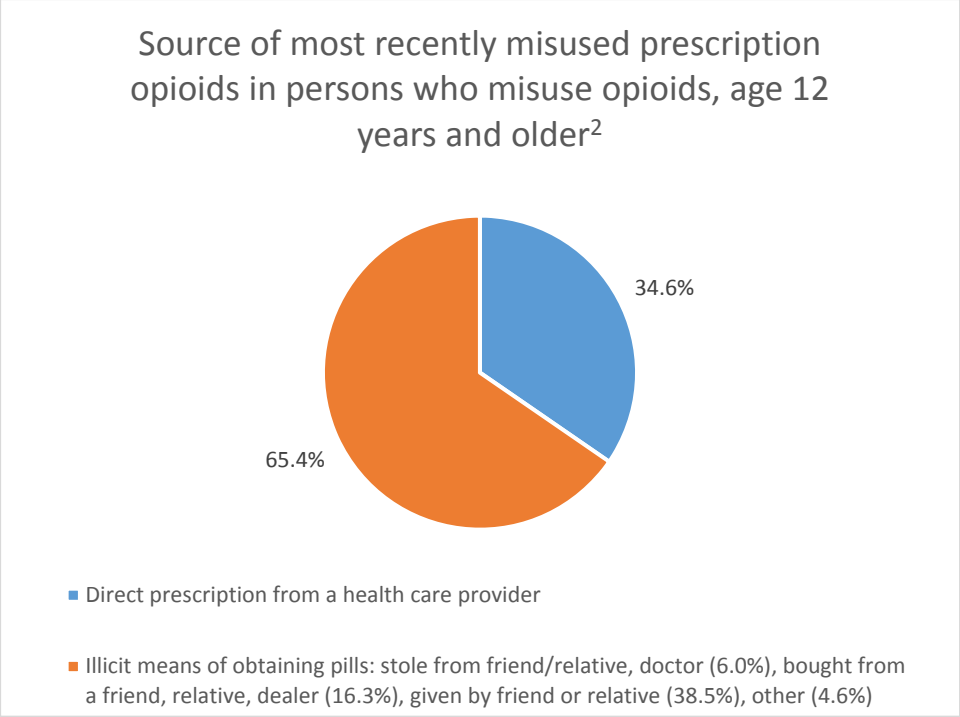

Figure 4. Sources of prescription opioids misused by persons age 12 and older who have misused opioids in the past year.[3]

There are some limitations to using NSDUH 2017 to estimate proportion of prescription opioids obtained directly from a health care provider versus some illicit source, in people with OUD who abuse prescription opioids. The Substance Abuse and Mental Health Services Administration (SAMHSA) expanded the definition of prescription opioid misuse in 2015.[55] Prior to 2015, "nonmedical use of prescription drugs" was defined as one that included only use of drugs not prescribed for the surveyee or only for the feeling that the drug caused. From 2015 onward, SAMHSA pivoted to "misuse," an umbrella term that included prior nonmedical users plus use in greater amounts or more often than as directed by a doctor. Currently defined "misusers" combine persons who use an extra pill infrequently for pain at one end of the spectrum of misuse, with persons with OUD who used opioids only maladaptively and suffer social and functional consequences as a result of their misuse, at the other end. It is

unclear how many of the 1/3 of misusers who obtain prescription opioids directly from their doctor are using them in the context of OUD, versus how many have an essentially stable chronic doses but take their pills outside of their prescribers direction infrequently.

NSDUH 2014,[56] the last results before the transition from reporting data for "nonmedical use" to that of "misuse," also reported on sources of misused prescription opioids, with some persons reporting >1 source. With person-source (as opposed to person) as the denominator, 1,109,000 of 5,418,000 (20.4%) nonmedically used prescription opioids were obtained directly from one doctor (derived from Table 6.49A of 2014 NSDUH detailed tables). Other sources included stolen from a friend, relative, or doctor (6.9%); bought from a friend, relative, or dealer (25.6%); given by a friend or relative (38.3%); multiple doctors ("doctor-shopping") or wrote fake prescription (5.3%); and other (3.3%). Saloner et al[57] examined NSDUH data from 2006 to 2013 and found that 23.7% of persons obtained nonmedically used prescription opioids directly from a physician, corroborating the 20.4% proportion when the denominator allows for multiple sources for the same person. Regardless of year, NSDUH data is limited to the non-institutionalized, non-imprisoned, non-homeless, household population, so members of these groups are not represented in these results. Exclusion of individuals residing in setting such as jails, institutions, or homeless shelters likely biases the proportion of misused opioids obtained from illicit sources down, such that the real proportion of misused opioids obtained via a direct prescription may be even less than 23.7% among all persons with OUD.

Regardless of the specific proportion, most persons who misuse prescription opioids, including those with OUD, do not obtain them via a legitimate medical channel (that is, a direct prescription from a health care provider dispensed from a legitimately supplied pharmacy). In a

small, qualitative study conducted in Delaware for which persons who abused or dealt opioids as well as other stakeholders (members of law enforcement, the Attorney General's office, state and city police departments) were interviewed, the authors concluded that the primary source of prescription drugs "on the street" were the elderly, pain patients, doctor shoppers, and dealers, who work with all of the former.[58] Cicero et al[8] examined prescription opioid diversion using data from SKIP and a separate study conducted in South Florida, the latter of which enrolled persons who reported the misuse of at least one prescription drug five or more times in the previous 90 days. Eligible subjects from either study were asked about what method they used to obtain each diverted prescription in the past 90 days, with many respondents reporting >1 source. The most prevalent (non-mutually exclusive) source of prescription opioids were dealers (66.6% of respondents), followed by sharing and trading with friends (54.6% of respondents), direct prescription from a doctor (13.8% of respondents), and prescription from a medical source that most likely was aware that the patient was misusing the pills ("pill mills," 12.5% of respondents). Persons with OUD who use prescription opioids can be sources of diversion themselves. Davis et al[9] analyzed data of a sample of street drug users and found that 46% of users of prescription opioids reported selling them. Among users of prescription opioids who also sold them who reported sources, 68.9% reported obtaining the pills directly from a doctor. This study was conducted in 2006 in New York City prior to availability of a state-wide PDMP (2013 in New York[60]), which has been shown to curb "doctor shopping" and the activity of "pill mills" in states where they have been implemented.[61-63]

9. Because people with OUD are prone to abuse of any substance, sometimes heroin use precedes, and sometimes it follows initiation of NMPOU.

Some of the studies cited by expert witnesses for the Plaintiffs* as evidence for a causal relationship between NMPOU and heroin use report the prevalence of heroin use in a sample of persons engaging in NMPOU,[28] or the prevalence of NMPOU in a sample of persons using heroin.[29-30] Interpretations related to the order of initiation of use (heroin versus prescription opioids as the first opioid of abuse) cannot be made, let alone those related to causality for heroin initiation, from such studies. Other studies cited report prevalence of OxyContin use in persons diagnosed with OUD,[31] or offer qualitative results only.[32-33] Cicero et al,[25] Siegal et al,[26] and Pollini et al[27] report the prevalence of NMPOU prior to heroin initiation among current heroin users, and since these studies do not include persons engaged in NMPOU who do not transition to heroin, incident *de novo* heroin use in this population cannot be derived from these reports. Studies that do report incidence of heroin initiation (*de novo* use) are confounded by polysubstance abuse accompanying the NMPOU that precedes the heroin use. Muhuri et al[23] reported that up to 86.1% of heroin initiates with prior NMPOU reported prior illicit drug (marijuana, cocaine, hallucinogens, inhalants). Banerjee et al[24] reported baseline NMPOU use (12.8% short term, 20.7% long-term) but also marijuana use (19.3%), stimulant use (28.3%), cocaine use (34.2%), and unhealthy alcohol use (17.6%) in heroin initiators, without reporting heroin initiation in those with isolated NMPOU. Similar to Muhuri et al, Cerdà et al[64] used NSDUH data from 2004 to 2011 to examine factors associated with heroin initiation in 12 to 21 year olds. These authors report that 36% of the included sample used drugs/alcohol other than heroin or prescription opioids, however did not account for prior polysubstance abuse when they reported heroin use by NMPOU. Grau et al[22] reported that 56.5% of the sample of subjects engaged in NMPOU had consumed alcohol to the point of intoxication, and

83.1% had used marijuana. Again, this confounding substance abuse was not accounted for in the analysis such that the reported incident heroin use cannot be interpreted as an isolated NMPOU-heroin initiation relation.

While the incidence of heroin initiation following isolated NMPOU cannot be easily abstracted from studies to date due to confounding by polysubstance abuse, there is some evidence that among persons with OUD, regardless of other substances used, heroin now surpasses either hydrocodone or oxycodone as the first opioid of abuse in opioid initiators. Cicero et al[64-65] trended the first opioid used in persons with OUD in a sample from the SKIP study between 2005 and 2015. Heroin as the first opioid increased from 8.7% in 2005, to 31.6% in 2015. In contrast, hydrocodone as the first opioid decreased from 42.4% to 24.1%, and oxycodone as the first opioid decreased from 42.4% to 27.8%, between 2005 and 2015. Figure5 provides more details about choice of first opioid for the intervening years. These findings support that addiction is a disease of the brain, and not necessarily a sequelae of the drug environment, and that the addicted brain will find substances to abuse via the most accessible route available. As opioid medications are becoming less available to buy or steal, so the population with SUD that may have at one point initiated opioid use by illegally buying or stealing opioid medications is now initiating opioid use by buying illicit street drugs such as heroin and related opioids.

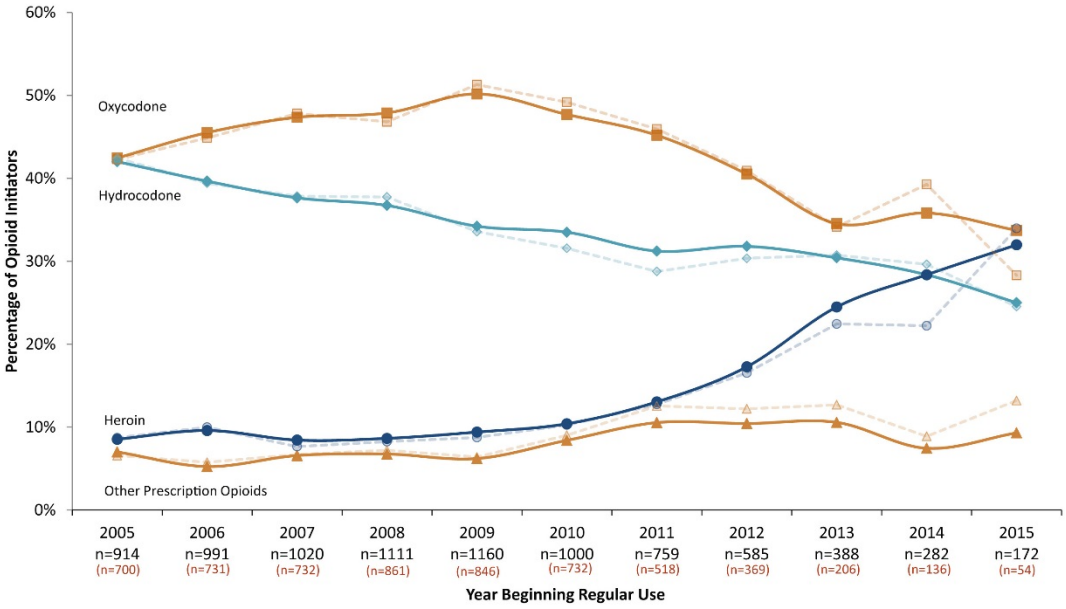

Figure 5. First opioid of regular abuse among opioid initiates with OUD, 2005 to 2015.[65]

10. The majority of opioid-related deaths are caused by heroin and other illicit opioids, with a growing proportion of those caused by fentanyl.

Ruhm[67-68] examined trends in deaths due to all drugs including opioid analgesics and illicit opioids, with cause-of-death for cases obtained from Multiple Causes of Death (MCOD) files from the CDC, between 1999 and 2015. He reported differing patterns in deaths due to opioid analgesics versus illicit opioids such as heroin. Deaths due to opioid analgesics rose rapidly from 1.3 to about 5 deaths per 100,000 between 1999 to 2011, declining to 4.8 deaths per 100,000 between 2011 and 2012 and remaining at that level since. In contrast, deaths due to illicit opioids rose slowly from 1.2 to 2.1 deaths per 100,000 between 1999 and 2006, and then more rapidly. By 2013, deaths due to illicit opioids had surpassed deaths due to opioid analgesics, and in 2015, deaths due to illicit opioids had reached 7.4 per 100,000 and accounted for 61% of all opioid-related deaths. A limitation of these findings is that opioid analgesic

deaths cannot be presented in sub-groups by those caused by illicitly obtained opioids through buying them from a dealer or sharing versus those in persons taking stable doses for pain.

Available illicit opioids available on the street are becoming increasingly deadly in large part due to the inclusion of synthetic opioid compounds, namely fentanyl and fentanyl analogs (including carfentanil, furanylfentanyl, acetylfentanyl). O'Donnell et al[69] reviewed opioid-related deaths in 10 US states reporting to the State Unintentional Drug Overdose Reporting System (SUDORS) between July and December 2016. These authors found that 56.3% of opioid related deaths tested positive for fentanyl, and 14.0% of opioid related deaths tested positive for fentanyl analogs. Using National MCOD data, Jones et al[70] reported that 45.9% of opioid-related deaths in 2016 involved fentanyl. Since fentanyl is not present in prescription opioid analgesic pills prescribed in a legitimate medical setting and dispensed through a licensed pharmacy, data on fentanyl-positive deaths highlight that the most tragic component of the opioid crisis – that is, the opioid-related deaths – are occurring in persons who do not obtain their abused substance from, nor likely interact at all with, the controlled clinical environment in which patients with pain are treated with stable doses of opioid analgesia.

In parallel with the rise in heroin, fentanyl, and other illicit opioid-related deaths, deaths from stimulants including amphetamine and cocaine have also been on the rise. According to the CDC, age-adjusted cocaine-related death rates increased 52.4% and psychostimulant-related deaths rose by 33.3% between 2016 and 2017.[71] Figures 3a, 3b, and 3c above demonstrate how the rise in amphetamine- and cocaine-related deaths echo the rise in opioid-related deaths. The "opioid" crisis appears to be more of a substance abuse crisis in general, with deaths from multiple substances on the rise.

11. Of opioid-related deaths in people who had used prescription opioids, most involved another concomitant substance such as benzodiazepine.

Kandel et al[72] examined changes in prescription opioid overdose deaths between 2002 and 2015 using data from the National MCOD files. Among opioid-related deaths in 2014-2015 in part due to prescription opioids, 57.9% involved another substance including benzodiazepines, antidepressants, heroin, alcohol, or cocaine. Like other studies using MCOD files,[67-68] these results cannot be presented in subgroups by whether or not the prescription opioids or concomitantly found benzodiazepines used by the decedent were prescribed by a health care provider, or were obtained illegally obtained and misused. We know that the many of these prescription-opioid-related deaths involved substances that could not have been obtained in a controlled clinical setting including 15.4% of deaths that involved heroin, 13.7% that involved alcohol, and 10.1% that involved cocaine (these proportions are not mutually exclusive, with ≥3 substances involved in some deaths).

While we cannot know whether prescription opioid deaths reported from MCOD data are prescribed or obtained illicitly and misused, other studies using alternative data sources have examined rates of overdoses in prescriptees enrolled in commercial health plans (i.e., we know the source of the culprit opioids in these cases). Kay[73] et al used data from a large nationwide claims database to quantify the change in the rate of opioid related emergency department visits (EDVs) and hospitalizations occurring in persons prescribed chronic opioids (>90 days supply) between 2009 and 2015. The rate of opioid-related EDVs decreased from 85 per 100,000 persons prescribed chronic opioids in 2009 to 73 per 100,000 in 2015, and the rate of opioid-related hospitalizations decreased from 168 per 100,000 in 2009 to 103 per 100,000

in 2015. In contrast, rates of opioid-related EDVs and hospitalizations were reported as *increased* by 99.4% and by 64.1%, respectively, between 2005 and 2014, by the Healthcare Cost and Utilization Project (HCUP).[74] The sample reported in the Kay study was restricted to persons prescribed chronic opioids, whereas the HCUP data was not and likely included persons who were taking prescription opioids illicitly. The fact that the rate of opioid-related EDVs and hospitalizations in persons prescribed chronic opioids is declining, but the rate of opioid-related EDVs, hospitalizations, and deaths in the population in general is increasing, supports the contention that a growing proportion of prescription opioid-related EDVS, hospitalizations, and deaths are occurring increasingly in persons obtaining the pills illicitly and using them in unsanctioned doses.

12. People with OUD are under-engaged for rehabilitation and treatment of their disease. Resources are out-matched by the number of persons requiring treatment, and treatment facilities that are available do not always use proven effective therapies for OUD, especially Medically Assisted Treatment (MAT).

Options for MAT now include opioid antagonists, including naltrexone, partial agonists (buprenorphine), and opioid agonists (methadone).[75] Studies have demonstrated an association between availability of treatment programs offering MAT and a reduction in heroin-related deaths.[76] Despite the increase in opioid-related deaths and the effectiveness of MAT, about 9% of drug treatment facilities offered any medication treatment for OUD between 2006 and 2016.[77] Because persons with OUD are commonly engaged in illicit activity in their quest to obtain the next dose of the abused substance, they often interact with law enforcement, and are sentenced in drug courts. Despite the opportunity inherent in an addicted person's coming

before public officials for potential triage into treatment, political and administrative barriers preclude the effective use of MAT in drug courts to manage addiction in offenders with OUD.[78] Peters et al[79] reported on coverage rates for OUD in health insurance plans in 6 cities and found that 29% of programs did not cover naltrexone for OUD with only 54% offering it in their tier 1 formulary list, compared to 6% and 78%, respectively, for naltrexone when use to treat alcohol use disorder. Even when a patient is initiated on an MAT regimen, studies have found that retention in therapy is variable, with duration of therapy often too short to optimize probability for success.[80-81] Barriers such as stigma surrounding treatment for addiction, small number of treatment centers offering MAT, lack of engagement by drug courts in using MAT, coverage of MAT by commercial insurers, and variable retention in MAT programs all have resulted in undertreatment of persons with OUD. Saha et al[82] examined prevalence and treatment for persons with non-medical opioid use disorder (NMPOUD) using NESARC data and found that only 17.7% of such persons were treated.

13. Efforts to mitigate the opioid crisis, such as state-level PDMPs, have been associated with decreases in the supply of opioids. Because such efforts do not target persons with OUD, the majority of whom do not obtain opioids from such settings, these efforts have had minimal impact on opioid-related death rates.

While the availability and quality of implementation of programs that include MAT remain lackluster, resulting in woeful undertreatment of persons with OUD, there have been efforts directed elsewhere in an attempt to mitigate the opioid crisis. Currently, 49 states have PDMPs, which have been found to reduce both the number of opioid prescriptions issued and new diversion cases. In many states where PDMPs and other policy initiatives aimed at curbing

prescribing and dispensing of prescription opioids, the number of prescriptions for opioids have declined.[63] Bao et al[83] used data from the National Ambulatory Medical Care Survey (NAMCS) to examine differences in rates of opioid prescription for persons presenting to an office-based physician for pain, between states that had implemented a PDMP by the time of the study and states that had not. Clinic visits included in the analysis occurred between 2001 and 2010. The authors found that the probability of an opioid prescription decreased from 5.5% to 3.7% (a relative reduction of 30%), before to after PDMP implementation. In Florida, establishing a PDMP and eliminating dispensing of opioid prescriptions directly from doctor's offices was associated with a reduction in new diversion investigations.[84]

While reductions in opioid prescribing in association with PDMPs and other policy initiatives have been demonstrated, relationship between these changes and reduction in opioid-related deaths has been harder to demonstrate. Patrick et al[85] examined whether annual opioid-related death rates per state were associated with state-level PDMP implementation between 1999 and 2013, and demonstrated a statistically significant reduction of 1.12 deaths per 100,000 in states before and after implementation. However, the opioid-related death rate in 2017 was 12.2 per 100,000,[67-68] so a reduction of 1 death is only a relative decrease of 9%. Other researchers have found mixed results when examining the relation between PDMP implementation and reduced opioid-related mortality, including mixed results in some reviews cited by expert witnesses for the Plaintiffs* as support for the efficacy of PDMPs in terms of opioid-related mortality. A review of 17 studies examining the relationship between PDMP implementation on fatal and/or non-fatal opioid overdoses demonstrated that such studies varied in quality (particularly, risk-of-bias).[86] The authors pooled the results of

these studies and modeled the relation between PDMP implementation (vs no PDMP implementation) and opioid-related deaths per 100,000. Before adjustment, PDMP was associated with an *increase* of 2.35 deaths per 100,000. After adjusting for fixed state effects including unemployment and educational attainment, year of legislation enacting a PDMP, and linear time to account for lag in time before effects of PDMP implementation become apparent, PDMP implementation was not associated with a significant reduction in opioid-related deaths. Haegerich et al [87] reviewed the literature for evaluations of state policy or systems-level interventions (including PDMPs) on provider behavior, patient behavior, and health outcomes. These authors found variability in the effect of each intervention on these outcomes. For PDMP availability as the intervention, findings from 6 studies were consistent with decreased use of schedule II (opioid) drugs by providers, but 3 studies found no change in provider behavior. Two studies found a significantly decreased use of multiple prescribers or pharmacies by a single patient in association with PDMP availability in the state. One study found an association between PDMPs and reduced substance abuse treatment admissions while two demonstrated no difference, and one found a significant reduction in oxycodone poison control center report rates. One study found no significant relation between PDMP and drug overdose mortality.

In general, use of PDMPs along with other state/system level interventions have been association with reduction in prescription of opioids. According to IQVIA, 72.4 opioid prescriptions per 100 person in the US were written in 2006. This number increased by 3% per year until 2010, after which it began to decline, first slowly (1.6% per year until 2014) and then more rapidly (8.2% per year between 2014 and 2017). By 2017, the number of opioid prescriptions written was 58.5 per 100 persons, an absolute reduction of 13.9 prescriptions and

a relative reduction of 19%.[5] Meanwhile, the opioid-related death rate has continued to climb with no apparent slowing. The National Institute of Drug and Alcohol Addiction (NIDA) reported that opioid-related deaths have continued to increase and in 2017, 60,977 persons died of an opioid-related cause; of these 43,948 (72% were heroin or fentanyl) and 17,029 (27.9%) from prescription opioids (Figure 6).[88]

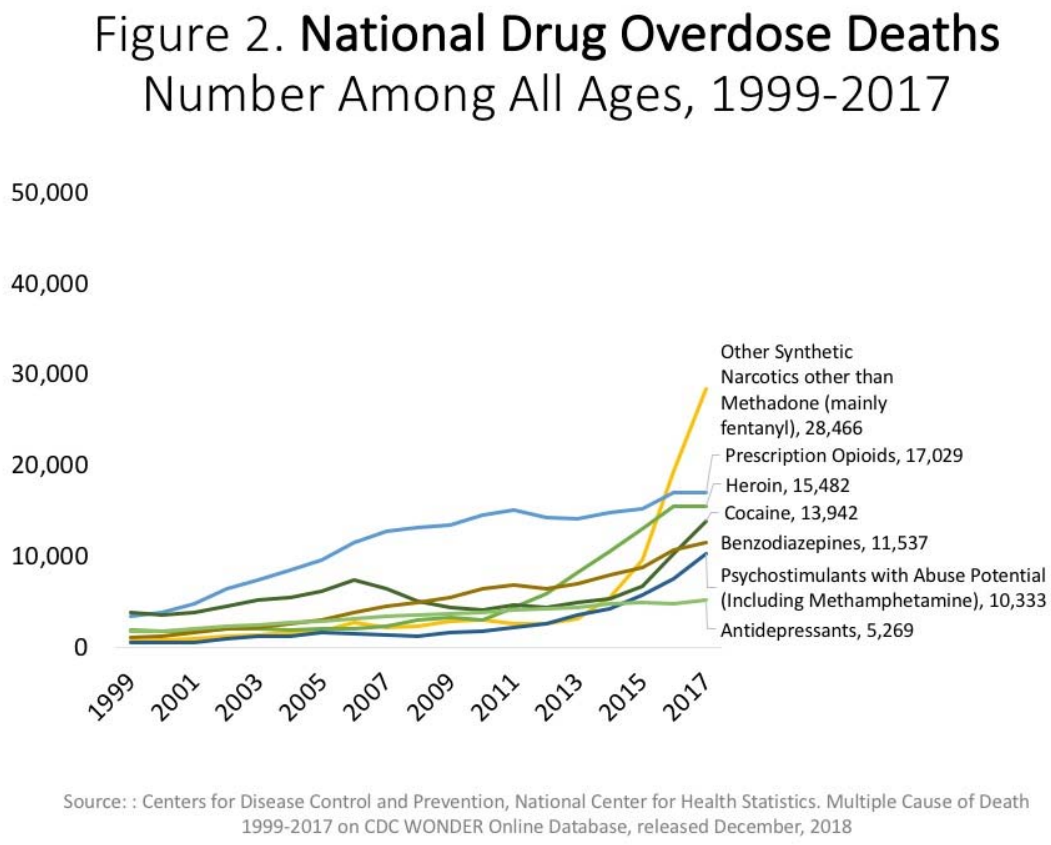

Figure 6. Overdose death rates.[88]

State/system level attempts to mitigate the opioid crisis seem to have defined the target population as persons prescribed opioid analgesia in a controlled clinical setting. Such a definition is low in sensitivity, as most people who engage in NMPOU or who have OUD do not obtain their opioids in this context, and low in specificity, as most people prescribed stable

doses of opioids for pain do not have OUD. Ali et al[89] examined state-level NSDUH data from 2004 to 2014, to compare opioid misuse and heroin initiation in states with versus without PDMPs. Past-year NMPOU, past-year prescription opioid dependence, and past year initiation of NMPOU did not undergo any significant reduction or increase relative to PDMP implementation. Past-year heroin use (yes/no), past-year dependence (yes/no), and past-year heroin initiation (yes/no) was not associated with PDMP implementation. PDMP use was associated with 10 to 20 fewer days of NMPOU in the past year, and PDMP use without any enhancements (such as mandatory access by prescribers) was associated with increased number of days of heroin use in the past year. So while PDMPs were associated with fewer days abuse of prescription opioids and more days use of heroin among people who were already abusers of these, PDMP implementation was not associated with fewer people engaging in NMPOU nor was it associated with more people using heroin.

Concluding remarks

Other countries have also experienced high rates of opioid-related deaths (see Figure 3c). In these countries, interventions that target persons with OUD have been effective in keeping opioid-related death rates from rising to level they are currently in the US. In Canada, naloxone became available without a prescription in 2016; as of 2018 in the US, 36 states still have existing laws making the possession of naloxone without a prescription illegal.[90] In British Columbia, which has been particularly impacted by the fentanyl overdose crisis, naloxone is available free of charge. The Canadian government has also passed legislation facilitating the institution of medically supervised injection facilities, which have been shown to rates of fatal overdoses by 30% in communities with high prevalence of injection drug use.[91] Instead of

focusing only guidelines circumscribing opioid analgesia for people with pain in a controlled clinical setting, British Columbia has developed a guideline for evidence-based treatment of OUD, which includes such recommendations as avoidance of referral for "detoxification" without addiction treatment in follow-up. Opioid agonist medications are provided free-of-charge to low- and middle-income persons in British Columbia, and funding has recently been provided for anonymous drug testing services so users of street drugs can detect fentanyl in any substance they plan to consume. Figure 7 compares the OUD deaths per 100,000 in the US and Canada.

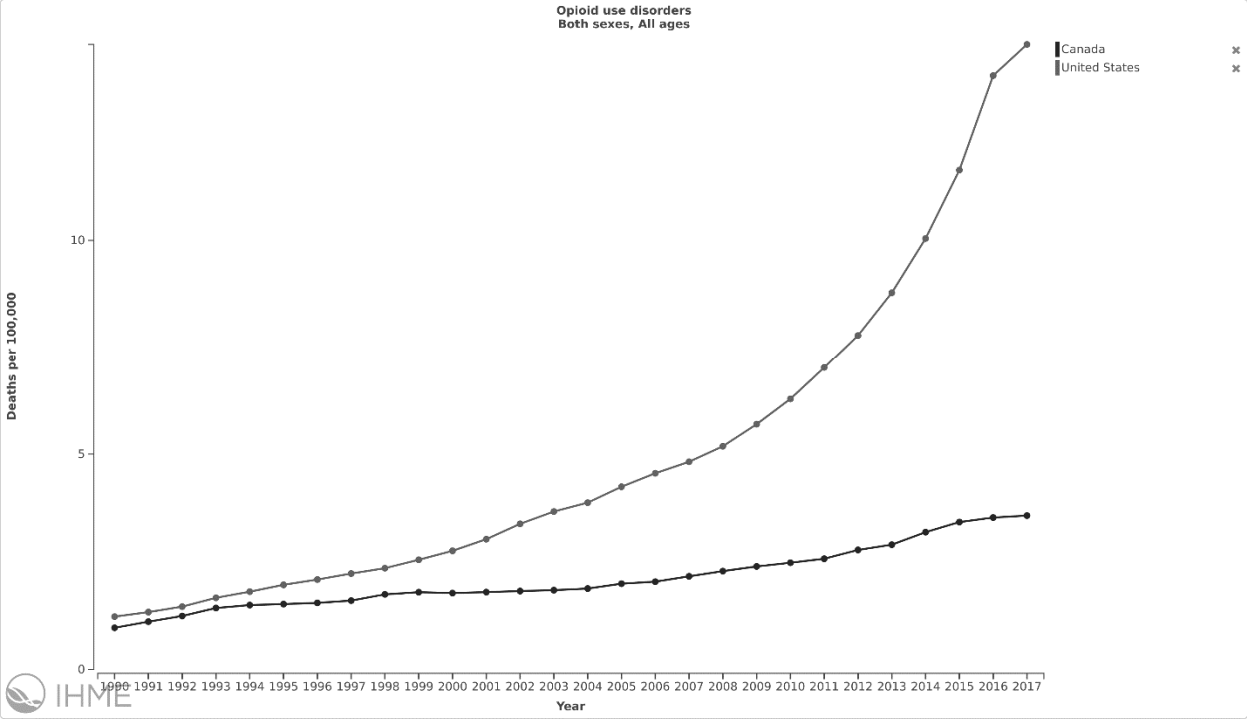

Figure 7. OUD Deaths in the US and Canada.[49]

Persons with OUD suffer from a disease of the brain, the mitigation of which will require increases in the enrollment in and quality of substance abuse treatment programs, to include employment of MAT. While some people prescribed opioids for pain develop *de novo* OUD[9] and continue to obtain their abused opioids directly from a healthcare provider, most people

with OUD obtain the abused prescription opioids illicitly, abuse illicit opioids such as heroin or fentanyl, or both. Many such people will abuse other drugs as well, despite the disruptive life consequences of that use (the definition of a substance use disorder), and despite a high risk of overdose and death. The addicted brain is masterful at obtaining the next dose of the substance upon which it is dependent, and untreated persons with OUD can be expected to continue to obtain opioids, increasingly illicitly if necessary, unless they are identified and enrolled in treatment. If we continue to direct our mitigation efforts toward persons without OUD who use opioids in stable doses for pain in a controlled clinical setting, we will continue to suffer the consequences of alarmingly high opioid-related death rates in the disparate population of persons with OUD.

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Submitted by Catherine Rahilly-Tierney MD, MPH

May 10, 2019

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Other Materials Considered

1. Corrected Second Amended Complaint and Jury Demand. Reviewed August, 2018.

2. The President's Commission on combating drug addiction and the opioid crisis. November 1, 2017.

3. Dispensing controlled substances for the treatment of pain. September 6, 2006.

4. Expert Report of Professor David Cutler, dated March 25, 2019.

5. Expert Report of Professor Jonathan Gruber, dated March 25, 2019.

6. Caleb Alexander, MD, MS, Supplemental Expert Witness Report. Submitted April 3, 2019.

7. Katherine Keyes expert witness report. Submitted March 24, 2019.

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Curriculum Vitae

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Place of Birth: Rochester, New York

Education

1997	B.A.	Anthropology, Biology	University of Pennsylvania College of Arts and Sciences, Philadelphia, Pennsylvania
2002	M.D.	Medicine	University of Rochester School of Medicine and Dentistry, Rochester, New York
2007	M.P.H.	Epidemiology	Harvard School of Public Health (HSPH), Boston, Massachusetts

Postdoctoral Training

07/2002-06/2005	Resident	Internal Medicine	Mount Sinai Medical Center, New York, New York
07/2005-06/2007	Fellow	Faculty Development and General Internal Medicine	Harvard Medical School (HMS), Boston, Massachusetts
07/2007-01/2009	Fellow	Preventive Cardiology	Veterans Affairs (VA) Boston Healthcare, Boston, Massachusetts

Faculty Academic Appointments

01/2009-	Instructor	Medicine	Harvard Medical School
01/2014-	Instructor	Medicine	Boston University Medical School

Appointments at Hospitals/Affiliated Institutions

07/2005-	Staff Physician	Medicine	VA Boston Healthcare
01/2009-	Associate Epidemiologist	Medicine (Division of Aging)	Brigham and Women's Hospital, Boston, Massachusetts

Other Professional Positions

1997-1998	Research Intern, Department of Neurology	University of Rochester School of Medicine and Dentistry
2012-	President and CEO, Strategic Research Partners LLC (formerly CRT Epidemiology Consulting LLC)	Clients in biotechnology and pharmaceutical industries and state and local governments/departments of health

Major Administrative Leadership Positions

2006-2009	Fellows' Meeting Coordinator	VA Boston Healthcare
2006-2013	Director, Preventive Cardiology Program	VA Boston Healthcare-Brockton branch

Committee Service

2004-2005	Advancing Idealism in Medicine	Mount Sinai Medical Center

Professional Societies

1998-2002	Physicians for Social Responsibility	Director, Teaching Day Committee
2005-	Society of General Internal Medicine	Member
2011-	American Heart Association	Professional Member

Editorial Activities

Ad hoc Reviewer

British Medical Journal

Annals of Internal Medicine

Honors and Prizes

1998	Albert and Phyllis Weber Scholarship	University of Rochester School of Medicine and Dentistry	Academic achievement

Report of Local Teaching and Training

VA Boston Healthcare

2007-	Management of Low Density Lipoprotein Cholesterol (LDL-C) Housestaff and medical students	One hour lecture
2008-	Management of High Density Lipoprotein Cholesterol (HDL-C) Housestaff and medical students	One hour lecture
2008-	How to read a methods section: Case of a meta-analysis of studies examining rosiglitazone and cardiac events Housestaff and medical students	One hour lecture

2009-	Do older patients benefit from LDL-C reduction? Housestaff and medical students	One hour lecture
2011-2013	Launching first-author projects in Observational Cohorts Preventive Cardiology fellows	One hour lecture
2012-	Management of hypertriglyceridemia Housestaff and medical students	One hour lecture

Harvard School of Public Health

2011	Observational database applications for outcomes research Visiting clinical and research fellows	3-hour workshop

Clinical Supervisory and Training Responsibilities

2005-2006	Urgent Care Preceptor, VA Boston Healthcare	One session per week
2006-2013	Preventive Cardiology Clinic Preceptor, VA Boston Healthcare	One session per week
2006-	Internal Medicine Ward Attending, VA Boston Healthcare	2 weeks per year
2013-	Primary Care Provider, VA Boston Healthcare	2 sessions per week

Laboratory and Other Research Supervisory and Training Responsibilities

2009-2013	Mentoring of Preventive Cardiology fellows, VA Boston Healthcare	Weekly mentorship of one or more fellows

Formally Supervised Trainees and Faculty

2009-2011 Raghava Velagelati, MD, Cardiology fellow, Baystate Healthcare System, Springfield, Massachusetts

Under my supervision Raghava is preparing a manuscript relating to changes in lipid parameters and incident congestive heart failure.

2011-2018 Peter Ofman, MD, Preventive Cardiology Fellow, VA Boston Healthcare

Under my supervision, Peter has published two first-author publications (one in *Circ Arrythm Electrophysiol)* and a third is in the code-checking phase.

Local Invited Presentations

No presentations below were sponsored by outside entities.

2010 Update on LDL-C management in primary care

Brockton VA Ambulatory Care department, VA Boston Healthcare

Report of Clinical Activities and Innovations

2003 Diplomate, National Board of Medical Examiners

2003-2005 New York State Medical License

2005- Massachusetts Medical License

2006 Diplomat, Internal Medicine, American Board of Internal Medicine

Report of Education of Patients and Service to the Community

No presentations below were sponsored by outside entities.

1999 Kids Adjusting Through Support, Rochester, New York

Weekly counselling children of deceased or seriously ill parents.

1999 Melita House for Teenage Mothers, Rochester, New York

Weekly provision of support to teenage mothers and their children.

2004 Mother Theresa's Mission of Charity, Addis Ababa, Ethiopia

Provided medical care for 1 month to end-stage AIDS patients residing at the Mission

Report of current research activities

Currently, I spend the majority of my research time collaborating with staff in the Massachusetts Department of Public Health (MDPH) Injury Surveillance Program on two data linkage projects, as a contractor under Strategic Research Partners, LLC. In one, we are linking person-level records of all opioid overdose (fatal and non-fatal) attended by ambulance from the Massachusetts Ambulance Trip Information Services (MATRIS) database to emergency department records in the MDPH Systemic Surveillance database. We are using the linked data both to validate case definitions for overdose in these data sources, and to examine outcomes of persons who suffer from an opioid overdose in Massachusetts. In a separate project, we have linked person-level records from the Massachusetts Department of Transportation crash data system with hospital admission, emergency department, and observation stay claims records using case-mix data from Center for Health Information Analysis. We are using this linked data to examine associations between driving impairment from alcohol or drugs, and outcomes including traumatic brain injury, length of hospital stay, and hospital charges.

Report of Scholarship

Peer reviewed publications in print or other media

Research Investigations

1. Holloway RG, Courtright CE, **Rahilly CR**, Totterman SM, Shrier D. Magnetic resonance imaging in delayed brachial plexopathy following a clavicular fracture. *European Neurology*. 1998; 40:105-6.

2. Day DO, Courtright CE, **Rahilly CR**, Holloway RG, Donaghue P. Projecting site supply costs when planning for clinical trial participation. *Applied Clinical Trials*. 1998; June: 71-4.

3. **Rahilly-Tierney CR**, Nash IS. Decision-making in percutaneous coronary intervention: a survey. *BMC Medical Informatics and Decision Making*. 2008; 8:28.

4. **Rahilly-Tierney CR**, Sesso HD, Bowman TS, Djoussé L, Gaziano JM. Change in High-Density Lipoprotein Cholesterol and Incident Coronary Heart Disease in Apparently Healthy Male Physicians. *American Journal Cardiology*. 2008; 102:1663-7.

5. **Rahilly-Tierney CR**, Lawler EV, Scranton RE, Gaziano JM. Low-density lipoprotein reduction and magnitude of cardiovascular risk reduction. *Preventive Cardiology*. 2009; 12:80-7.

6. **Rahilly-Tierney CR**, Lawler EV, Scranton RE, Gaziano JM. Cardiovascular benefit of magnitude of low-density lipoprotein reduction: a comparison of subgroups by age. *Circulation.* 2009; 120:1491-7.

7. **Rahilly-Tierney CR**, Spiro A, Vokonas P, Gaziano JM. Relation between high-density lipoprotein cholesterol and survival to age 85 years in men (from the VA Normative Aging Study). *American Journal Cardiology*. 2011; 161:712-18.

8. **Rahilly-Tierney CR**, Sesso HD, Djoussé L, Gaziano JM. Lifestyle changes and 14-year change in high-density lipoprotein cholesterol in a cohort of male physicians. *American Heart Journal*. 2011; 107:1173-7.

9. **Rahilly-Tierney CR**, Arnett DK, North KE, Pankow JS, Hunt SC, Ellison RC, Gaziano JM, Djoussé L. Apolipoprotein ε4 polymorphism does not modify the association between body mass index and high-density lipoprotein cholesterol: a cross-sectional cohort study. *Lipids in Health Disease*. 2011; 10:167.

10. Robinson JG, **Rahilly-Tierney C**, Lawler E, Gaziano JM. Benefits associated with achieving optimal risk factor levels for the primary prevention of cardiovascular disease in older men. *Journal of Clinical Lipidology.* 2012; 6:58-65.

11. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, Manson JE, Qiao Y, Liu S, Merriam PA, **Rahilly-Tierney C**, Thomas F, Berger JS, Ockene JS, Curb JD, Ma Y. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Archives Internal Medicine*. 2012; 172:144-52.

12. **Rahilly-Tierney CR**, Vokonas P, Gaziano JM, Spiro AS III. Lifestyle change and high-density lipoprotein change: the VA Normative Aging Study. *Clinical Cardiology.* 2012; 35(7): 437-42.

13. **Rahilly-Tierney CR**, Sesso HD, Gaziano JM, Djousse L. High-density lipoprotein and mortality before age 90 years in male physicians. *Circulation Cardiovascular Quality and Outcomes.* 2012; 5(3):381-6.

14. Ofman P, **Rahilly-Tierney C**, Djousse L, Peralta A, Hoffmeister P, Gaziano JM, Weiss A, Lotan C, Rosenheck S. Pacing sytem malfunction is a rare cause of hospital admission for syncope in patients with a permanent pacemaker. *Pacing Clin Electrophysiol.* 2013 Jan; 36(1):109-12.

15. Ofman P, Khawaja O, **Rahilly-Tierney CR**, Peralta A, Hoffmeister P, Reynolds MR, Gaziano JM, Djousse L. Regular physical activity and risk of atrial fibrillation: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol.* 2013 Apr; 6(2):252-6.

16.Ofman P, Petrone AB, Peralta A, Hoffmeister P, Albert CM, Djousse L, Gaziano JM, **Rahilly-Tierney CR**. Aspirin use and risk of atrial fibrillation in the Physicians' Health Study. *J Am Heart Assoc*. 2014 June; 3(4).

17.Turner RR, **Rahilly-Tierney C**, Cowan D, Scranton R, Peura D. Belladonna alkaloid/phenobarbital (Donnatal) effective for treating IBS symptoms. *JJ Gastro Hepato.* 2014; 1(2):010.

18. **Rahilly-Tierney C**, Walton S. Cost-effectiveness of the 70-gene signature versus Adjuvant! Online and systemic chemotherapy for risk stratification of patients with node-negative breast cancer: Does accuracy matter? *J Clin Oncol.* 2015; 33(14): 1628-29.

19.Duh QY, Busaidy NL, **Rahilly-Tierney C**, Gharib H, Randolph GR. A systematic review of the methods of diagnostic accuracy studies of the Afirma Gene Expression Classifier. *Thyroid.* 2017; 27(10):1215-1222.

20.Duh QY, **Rahilly-Tierney C**, Gharib H. Exclusion of Eligible Indeterminate Thyroid Nodules in Estimates of Negative Predictive Value for the Gene Expression Classifier. *JAMA Otolaryngol Head Neck Surg.* 2017; 143(7):737-738.

Other peer-reviewed publications

1. Holloway RG, Benesch CG, **Rahilly CR**, Courtright CE. A systematic review of cost effectiveness of stroke evaluation and treatment. *Stroke.* 1999; 30:1340-9.

2. **Rahilly CR**, Farwell WR. Prevalence of smoking in the United States: A focus on age, sex, ethnicity, and geographic patterns. *Current Cardiovascular Risk Reports*. 2007; 1: 379-83.

Professional educational materials or reports, in print or other media

1. **Rahilly-Tierney CR**, Gaziano JM. Cardiovascular Risk Assessement: Materials for inclusion in educational binder for peers providing services in VA Boston Preventive Cardiology clinics. VA Boston Healthcare, 2013.